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Microneedle arrays for brain drug delivery: the potential of additive manufacturing

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Abstract

For a long time, the treatment of brain diseases has been a significant challenge. Drug delivery to the brain has recently become one of the most challenging problems for patients with severe forms of central nervous system diseases. The blood–brain barrier (BBB) poses a significant challenge for drug delivery to the brain. While extensive efforts focus on finding materials to overcome the BBB for brain tumor treatment, it limits the penetration of chemotherapeutic drugs for the broader treatment of brain diseases. The oral method of drug administration has several drawbacks, such as the loss of drugs because of metabolism and gastrointestinal environmental issues. Besides, using the intravenous route to administer medicines has several disadvantages, including discomfort at the injection site, infection, bleeding, anxiety, and incompetence toward patients. Fabrication and development of microneedles to overcome the drawbacks mentioned above of traditional drug delivery methods may be a viable alternative. Drug delivery using microneedle arrays (MNAs) has recently been shown to be an effective method for delivering drugs to the brain. Different fabricating methods like three-dimensional printing could be used for the fabrication of personalized drug delivery systems, like MNAs, with precise control over spatiotemporal drug distribution. This article presents a review of using MNAs for drug delivery to the brain.

Key words: microneedle array, drug delivery, brain, blood–brain barrier

1. Introduction

Drug delivery to the brain possesses a number of challenges, such as the blood–brain barrier (BBB)'s restrictive nature, limiting the entry of therapeutic agents. The BBB is composed of endothelial cells with tight junctions formed by astrocytes, pericytes, and the basal membrane (Daneman and Prat 2015). The delicate nature of brain tissue adds complexity, requiring precise and targeted delivery methods. Additionally, the potential for local toxicity and inflammation necessitates careful consideration in developing effective strategies. Overcoming these challenges is essential for enhancing the efficacy of brain drug delivery, improving patient outcomes, and advancing neurotherapeutics (Bors and Erdő 2019). Difficulties in delivering drugs to the brain are typically ascribed to the intricate and tightly regulated barriers that hinder medications from reaching their intended destinations within the brain after entering the body (Nance et al. 2022). The BBB has been extensively studied in the context of drug delivery (Ali and Chen 2015; Rustenhoven and Kipnis 2019; Zeynalzadeh et al. 2024). Functioning as a semipermeable and highly selective barrier, the BBB acts to separate the blood circulating in the body from the brain and the central nervous system (CNS). It tightly controls the flow of molecules into and out of the CNS, thereby regulating the chemical composition essential for proper brain function (Abbott et al. 2006; Oddo et al. 2019). The presence of this barrier poses challenges in delivering drugs to the CNS.

Despite the increasing prevalence of neurodegenerative disorders, there are limited effective treatments available, primarily due to the impediment presented by the impermeable BBB (Sweeney et al. 2018). Consequently, strategies to address the obstacles presented by the BBB are imperative. Administering therapeutic substances through the intranasal route offers a non-invasive approach for circumventing the BBB and deliver medications to the brain. This technology enables the swift delivery of drugs that typically encounter difficulty penetrating the BBB, reaching the CNS within minutes (Hanson and Frey 2008). Despite its benefits, intranasal delivery has certain limitations, including variations in nasal cavity shapes, challenges in precise dosing, mucociliary elimination, and drainage to the pharynx or lower regions (Wu et al. 2023). An alternative non-invasive approach involves ultrasound-mediated drug delivery, where ultrasound is used to temporarily open the BBB in specific areas of the brain.

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However, this method has constraints, such as the requirement for specialized equipment and the need for a trained operator, making it economically impractical beyond major hospital centers (Aryal et al. 2014).

Another approach to overcome the challenges in drug delivery to the brain is the local delivery of therapeutics to the CNS by using biocompatible and biodegradable materials placed within the tumor resection cavity (Han et al. 2019). Thus, continuous efforts are being made to develop and explore novel therapeutic strategies that can circumvent this barrier. These new approaches can be broadly categorized as localized and systemic drug delivery methods (Allhenn et al. 2012). Localized delivery of therapeutic agents into the brain involves methods like transcranial injections, implantation of chemotherapeutic materials, catheters connected to reservoirs, and convection-enhanced delivery, providing an alternative approach for treating brain diseases (Gabathuler 2010; Barua et al. 2016; Xu et al. 2020). One major advantage of localized delivery strategies is their ability to bypass the BBB naturally, enabling therapeutic agents to reach the target site with high bioavailability and minimal drug loss. Localized or topical administration of drugs has the potential to overcome challenges posed by different biological barriers encountered during drug delivery (Antimisiaris et al. 2021). Moreover, local delivery offers the benefit of exposing local lesions to sustained and effective concentrations of the therapeutic agent. Initial studies in this field focused on the use of biodegradable wafers infused with chemotherapeutic agents (Patel et al. 2012).

Currently, the Gliadel® wafer (carmustine wafer or bischloroethylnitrosourea wafer) is the only FDA-approved local treatment for brain tumors in the USA, commonly used after resection and in combination with other treatments (Chakroun et al. 2018). For many years, catheter drug delivery systems have been utilized clinically to enable intermittent bolus injections or continuous infusion of agents at the affected area (Hersh et al. 2016). An alternative method for treating malignant gliomas locally entails utilizing nanocarriers, including liposomes, polymeric nanocapsules, and solid lipid nanocapsules. These carriers, sized between 10 and 1000 nm, can be administered directly into the tumor site for targeted therapy. The advancement of nanocarrier implants seeks to combat multidrug resistance mechanisms on tissue and cellular fronts. Additionally, these systems are anticipated to bolster drug stability and enhance drug dispersion. Integrating localized administration routes with nanoparticulate formulations, such as liposomes, can present supplementary benefits. These include prolonged retention of elevated drug concentrations at the designated site, regulated release of the drug for sustained therapeutic outcomes, diminished risks of side effects and toxicity owing to localized drug concentrations, and fortified protection of drugs against adverse environmental conditions at the target site. Incorporating targeted liposomal formulations could amplify these therapeutic advantages even further (Antimisiaris et al. 2021).

Microneedles (MNs) have predominantly been employed for drug delivery to the skin. The skin can be fully regenerated within a few hours after using them (Mdanda et al. 2021). MNs have unique specifications, including painless penetration, minimal invasiveness, mild inflammation if any, excellent medicinal efficiency, and the ability to deliver very large substances characterized by ionic and hydrophilic physicochemical characteristics. Furthermore, MNs with possible outlets placed on the side can solve the blockage issue in conventional syringe needles (Lee et al. 2015). The first concept for using MNs for drug delivery was several decades ago, but they did not become the focus of serious research until the mid-1990s when microfabrication technology made them possible (Kim et al. 2012). Microneedle arrays (MNAs) are made up of micron-sized needles organized in arrays to deliver medications (Larrañeta et al. 2016; Waghule et al. 2019; Babu et al. 2024). MNAs for action disrupt the top layer of skin and create micron-sized pathways for delivering the drug to the epidermis or the upper dermis region (Sharma 2017; Waghule et al. 2019). The medication is initially given to the local tissue and then distributed throughout the body. Due to increased accumulation, the drug's effectiveness is enhanced within the local tissue (Khan et al. 2021). MNAs can be used to deliver small and macromolecules such as chemotherapeutics, genetic material, proteins, and nanoparticle-based anticancer medications (Moreira et al. 2019). Moreover, MNAs could deliver multiple drugs simultaneously and enable controlled release, thus efficiently optimizing or preventing interaction between multiple drugs.

In recent times, MNAs have been utilized for drug delivery into tissues beyond the skin. Recent studies have shown that they can be inserted into brain tissue to deliver medications as a potential treatment option (Lee et al. 2021). The presence of multiple protrusions within an MNA provides a solution for delivering drugs uniformly and with improved penetration. This is achieved by penetrating the brain tissue, adapting to the brain parenchyma, and remaining in place until the entire drug payload is released. These advancements represent substantial improvements compared to the technology utilized in the Gliadel® wafer. As a result, microneedles show immense potential as a technology for delivering drugs locally to the tumor resection cavity in the brain, especially in the treatment of tumor cells dispersed within the neural parenchyma (Muresan et al. 2023). Also, MNAs could be used to deliver the drugs to the brain transdermally and deliver the drug to the brain through the bloodstream (Kearney et al. 2016; Agrawal et al. 2018; Yan et al. 2020; Zhang et al. 2022; Zhou et al. 2022; Li et al. 2023). Furthermore, the MNAs could be used to deliver the drug to the brain intranasally (Permana et al. 2023; Ruan et al. 2024).

Considerable efforts have been made to find materials capable of crossing the BBB for brain tumor treatment. However, the BBB also hampers the penetration of chemotherapeutic drugs into brain tissue for the treatment of brain diseases (Banks 2016; Jiang et al. 2023). The MNAs have been fabricated through different methods like microfabrication and micromachining. The advancements in three-dimensional (3D) printing resolution, the precision of features, and the accessibility of affordable raw materials have made it possible to use 3D printing for producing various types of MNAs (Ogundele and Okafor 2017; Economidou et al. 2018; Park

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et al. 2019; Dabbagh et al. 2020). Compared to conventional methods, 3D printing techniques allow for the fabrication of more intricate and complex MNA structures (Han et al. 2020). With 3D printing technology, MNAs with different structures can be created in a single step, and the high resolution of the 3D printer ensures the formation of detailed arrays (Pere et al. 2018).

The present review aims to investigate the viability of utilizing microneedles for drug delivery to the brain. Initially, a concise overview of MNAs for drug delivery and their potential in addressing brain diseases is provided. Subsequently, the general attributes of MNAs, encompassing various types and the materials utilized in their construction, are examined. The discussion then delves into diverse manufacturing processes for MNAs. Lastly, a compilation of various applications of MNAs in previous studies is presented.

2. Microneedle arrays for drug delivery and their potential for treating brain diseases

Over the past two decades, there has been a strong focus on the development of MNAs as drug carrier materials to facilitate precise therapy for various tissues. Microneedles are miniature needles having a shaft length normally below 1000 μm and have garnered considerable attention in drug delivery studies because of their capability to be inserted into the tissue with less pain compared to traditional hypodermic needles. The use of MNA-based drug carriers has rapidly progressed as drug delivery systems due to their exceptional advantages, including minimal invasiveness, painlessness, ease of use, low risk of microbial penetration, and accelerated healing at the insertion site (Yu et al. 2015; McAlister et al. 2021; Mbituyimana et al. 2022; Haidari et al. 2024).

The introduction of MNA-mediated drug delivery has opened up new possibilities in cancer therapy. MNAs provide a local drug delivery method that reduces systemic drug exposure while enriching drug concentration at the site of the lesion, resulting in reduced side effects associated with therapeutic agents and improved treatment efficacy. Based on these characteristics, MNAs can be further developed to incorporate various functions for smart drug release, like light-responsive controlled release (Jiang et al. 2023). MNA-based drug carriers can deliver therapeutic materials such as cells, small compounds, and macromolecules including proteins, vaccines, and genes (Sullivan et al. 2010; Chang et al. 2021; Makvandi et al. 2021; Yin et al. 2021). MNAs can be categorized into different types, including solid, dissolving, hollow, coated, and hydrogel-forming MNAs (Shoffstall et al. 2018; Li et al. 2021). Dissolving microneedles are crafted by blending a polymer with specific qualities like biocompatibility and controlled dissolution alongside the chosen drug or nanoparticle (NP). Upon insertion into the tissue, the polymer dissolves gradually, thereby releasing the drug payload. This delivery method boasts numerous benefits, including the microneedles' biodegradability, which negates the requirement for surgical removal post-administration. They also ensure accurate anchoring at the resection site and maintain uniform and close contact with the brain parenchyma, thereby facilitating the diffusion of NPs into the targeted tissue. Microelectromechanical systems (MEMS) microneedles present competitive advantages over traditional needles. They allow for design flexibility, enabling outlets to be placed at the tip, and their smaller size allows for minimally invasive injections. Unlike traditional needles that may experience blockage due to outlet location at the tip's end, MEMS microneedles with side-placed outlets encounter fewer blockage issues. Moreover, their reduced size not only minimizes tissue damage during insertion but also enables precise targeting, especially in experiments involving small animals like mice (Lee et al. 2015). While research on using microneedles for insertion into other tissue types is limited, a recent study by Lee et al. (2021) demonstrated the feasibility of microneedles being inserted into brain tumors to deliver theranostic NPs and photons as a potential treatment option. As a result, microneedles hold significant promise as a technology for delivering NPs locally to the brain resection cavity, particularly for treating disseminated tumor cells in the neural parenchyma (Muresan et al. 2023).

3. General characteristics of microneedles

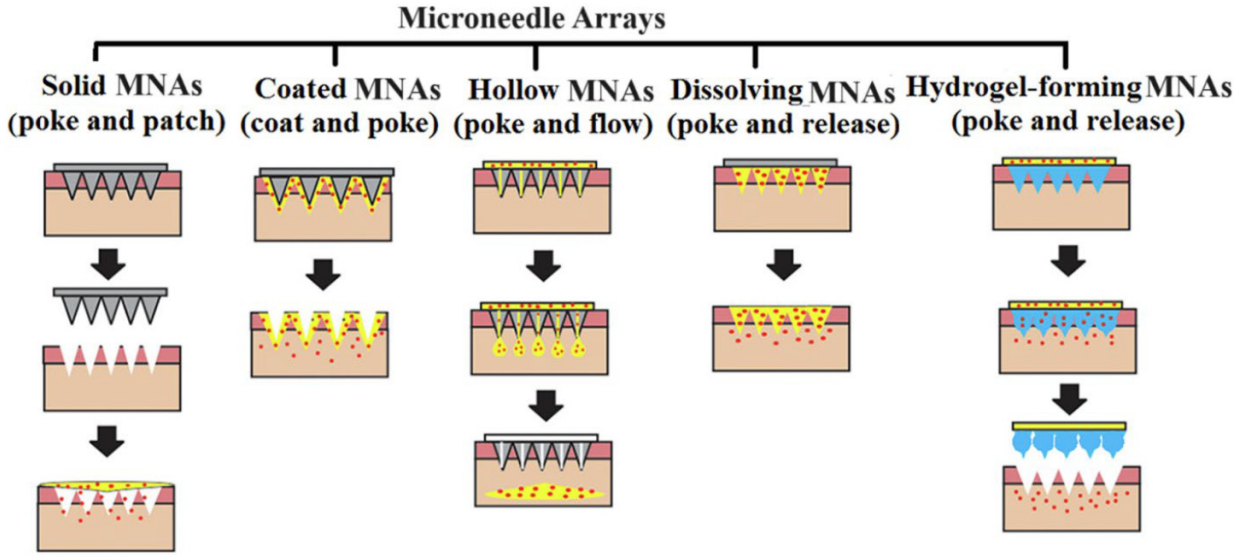
Microneedles arrays can be classified into distinct categories depending on several factors, such as their material composition, mode of operation, type of application, external structure, shape, and method of delivery (Khan et al. 2021). Below, various types of MNAs are described based on their mechanism of action and the materials they are made from.

3.1. Types of microneedle arrays based on their mechanism of action

Regarding the mechanism of action and drug delivery approach, MNAs can be categorized into five classes: solid, coated, hollow, dissolving, and hydrogel/swellable (Parhi and Supriya 2019). Solid MNAs are specifically designed to create micropores in the skin, enabling the medication to bypass the stratum corneum (SC) layer and reach the epidermis layer (Parhi and Supriya 2019). Once the micropores are formed, the medication can be applied to the location on the skin where the micropores were created, enabling distribution throughout the body (Yang et al. 2019). These MNAs can be provided for a one-step procedure application in which the medication is coated on the MNA and then inserted into the skin, or in a two-step procedure application in which the uncoated needle is inserted into the skin to create micropores, and then drug formulations are applied. In a one-step process, after removing the MNA, the medication remains deposited within the skin's membranes. In a two-step process, the drug is available in an individual formulation and moves through the micropores made by MNAs to the epidermal layer of the skin. The solid MNAs are normally between 150 and 300 μm in length with a wearing time between 30 s and 10 min (Parhi and Supriya 2019).

Coated MNAs serve two primary purposes: first, they pierce the skin, and second, they deliver the intended medication

Fig. 1. Various categories of microneedle arrays (MNAs), classified based on their mechanism of action and drug delivery approach; reprinted with permission from Elsevier (Al-Japairai et al. 2020).



that is applied on the surface of the microneedles (Yang et al. 2019). The coated MNAs are first coated with the medication before being applied to the skin, and a specific quantity of the medication can be delivered upon the insertion. In this manner, after puncturing the skin, the medication dissolves in the surrounding tissue, allowing the MNA to be removed from the application location (Chege et al. 2017). The limitation of coated MNAs is the low dose of the drug that they can deliver (Yang et al. 2019).

Hollow MNAs are normally designed with a drug reservoir containing a hole at the needle's center, primarily aiming to administer a relatively large dose of medication to address the limitation of coated MNAs. When a hollow MNA is inserted into the skin, the hollow bore can pierce the skin's SC layer and make a direct way into the epidermis layer. The hollow MNAs normally are expensive and require expensive fabrication methods (Parhi and Supriya 2019). However, one of the main issues of hollow MNAs is their risk of fracture because of their insufficient mechanical strength (Yang et al. 2019).

Dissolving MNAs are intended to break through the skin and establish channels for medications, then dissolve to allow other substances to enter through (Rejinold et al. 2016). This type of MNA is designed to release the medication after dissolving in the skin in some minutes without generating any sharp waste (Arya et al. 2017). Dissolving MNAs have been employed to deliver a wide range of substances., from hydrophilic, low molecular weight drugs to large biopharmaceutical molecules. The primary advantage of this type of MNAs is that they are biodegradable when they come into touch with the skin's interstitial fluid (ISF). It incorporates a one-step approach for patients' convenience (Parhi and Supriya 2019). Dissolving MNAs are made of safe materials, including biodegradable and natural polymers that can manage the release of drugs incorporated in the polymer (Yang et al. 2019).

Hydrogel forming/swellable MNAs represent the latest category of MNAs. These MNAs are composed of crosslinked hydrogels, and their mechanism of action differs from other types of MNAs. Upon insertion into the skin, they readily absorb tissue fluid due to the hydrophilic nature of the hydrogels, creating microchannels or pathways within the needle. These channels facilitate the diffusion of the drug into the microcirculation (Turner et al. 2021). Small hydrophilic medications and large molecular weight molecules are frequently delivered by this type of MNA. When compared to hollow MNAs, hydrogel or swellable MNAs offer superior control over chemical distribution in a precise dosage and are not impeded by dermal tissue. Additionally, hydrogel or swellable MNAs can be manufactured in various patch sizes and shapes, and they are sterilizable (Parhi and Supriya 2019). The drug molecules contained within the base plate may potentially permeate through the needles to the skin, unlike dissolving MNA systems. Moreover, by adjusting the degree of crosslinking within the hydrogel structure, the rate of drug delivery can be finely adjusted (Chege et al. 2017). Figure 1 depicts the classification of MNAs based on their mechanism of action and approach to drug delivery (Al-Japairai et al. 2020).

3.2. Types of microneedle arrays based on their materials

MNAs have been fabricated using a variety of materials, such as metals including titanium (Li et al. 2017), stainless steel (Rajabi et al. 2016; Vinayakumar et al. 2016; Jung et al. 2017), silicon (Lee et al. 2015; Pennathur et al. 2020), ceramics (Boks et al. 2015), biodegradable polymers like polylactic acid (PLA) (Nguyen et al. 2019), poly(lactic-co-glycolic acid) (PLGA) (He et al. 2020), polyglycolic acid (PGA) (Chen et al. 2020), non-degradable polymers like photolithographic epoxy (Stavrinidis et al. 2016), and hydrogels (Turner et al. 2021). When it comes to MNA materials, it is important for

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them to possess suitable mechanical properties to penetrate the skin (Dharadhar et al. 2019). For non-dissolving MNAs, the materials should be inert and biocompatible to avoid triggering an immune response. Conversely, for coated and dissolving MNAs, the materials should typically be water-soluble and biocompatible. Moreover, they need to dissolve or disintegrate within the body without causing any toxicity. Ensuring compatibility between the MNA material and the drug is essential to maintain specifications throughout the manufacturing, storage, and transportation processes (Jung and Jin 2021). Below are descriptions of the properties of some well-known materials used in MNAs.

3.2.1. Silicon

Silicon remains the predominant material used in MNAs (Rad et al. 2021). Its mechanical strength is suitable for skin penetration, making it a popular choice for producing solid and coated MNAs (Hoang et al. 2015). The fabrication process allows for the creation of small, sharp-tipped silicon MNAs, some as short as 100 μm, with precise accuracy (Li et al. 2019). However, there is a safety concern if the silicon MNA breaks during application and fragments remain in the tissue. In addition to solid MNAs, silicon has more recently been utilized in reverse master molds (Lutton et al. 2015).

3.2.2. Metals

MNAs are produced from metals such as stainless steel, titanium, nickel, and palladium. Despite some toxicity issues, metallic MNAs have better mechanical properties and biocompatibility than silicon MNAs (Rad et al. 2021). Metals can be used to produce solid, coated, and hollow MNAs. Typical metallic materials that are used to produce MNAs are stainless steel and titanium. Stainless steel is more common and more cost-effective than titanium. On the other hand, Ti alloys have higher mechanical properties and corrosion resistance than stainless steel (Jung and Jin 2021).

3.2.3. Polymers

In recent times, the pharmaceutical industry has witnessed numerous investigations into polymeric MNAs, specifically dissolving and hydrogel/swellable types, for drug delivery purposes (Cheung and Das 2016; Hao et al. 2017). Polymeric materials have garnered significant interest due to their favorable characteristics, such as biocompatibility, strong mechanical properties, cost-effectiveness, biodegradability, and relatively low fabrication costs (Prausnitz 2017; Rad et al. 2021). Dissolving or hydrogel/swellable MNAs have been successfully developed using various types of polymers, including hydroxypropyl methylcellulose (Kim et al. 2016), hyaluronic acid (HA) (Du et al. 2019), carboxymethyl cellulose (Mistilis et al. 2015), polyvinyl pyrrolidone (Caffarel-Salvador et al. 2015; Tas et al. 2017; Tang et al. 2018), PLGA (Li et al. 2019), poly (methyl vinyl ether co-maleic acid) (Parhi and Supriya 2019), and hydrogels (Wang et al. 2017; Chang et al. 2021). Hydrogels, in particular, exhibit desirable mechanical properties in their dry state, allowing them to be easily inserted into the skin while maintaining their structure when swollen and remaining intact during removal (Wang et al. 2017).

3.2.4. Glass

Glass was primarily used to fabricate hollow MNAs (Dharadhar et al. 2019). Glass MNAs display adequate strength for skin penetration, enabling easy processing of the tapered shape. They are easy to sterilize due to their stability at high temperatures and pressure. However, Glass MNAs break easily; specifically, they can cause inflammation or granulomas if the tips of the MNAs are broken and remain in the skin tissue (Jung and Jin 2021).

3.2.5. Ceramics

Ceramic materials like calcium phosphate, alumina, and calcium sulfate are biocompatible and have good mechanical properties. Various investigations have explored their use in the fabrication of MNAs (Ita 2018).

4. Additive manufacturing of microneedle arrays

Conventionally, MNAs have been manufactured through microfabrication and micromachining. Traditional manufacturing of MNAs involves a number of tedious and difficult-to-extend processes (Zhu et al. 2020). Besides, MNAs on curved surfaces are difficult to fabricate using conventional methods (Yang et al. 2019). Advancements in 3D printing resolution, precise feature fabrication, and the availability of cost-effective raw materials have enabled 3D printing to produce various types of MNAs (Ogundele and Okafor 2017; Economidou et al. 2018; Park et al. 2019; Dabbagh et al. 2020). Compared to conventional methods, 3D printing techniques allow for the creation of more sophisticated and complex MNA structures (Han et al. 2020). Utilizing 3D printing technology, MNAs with diverse structures can be fabricated in a single step, and the high resolution of the 3D printer ensures the detailed formation of arrays (Pere et al. 2018). Various 3D printing methods, such as digital light processing (DLP), high-precision stereolithography (SLA), and fused deposition modeling methods, have been employed to manufacture MNAs (Luzuriaga et al. 2018; Johnson and Procopio 2019; Economidou et al. 2021). Lim et al. (2017) introduced a novel 3D-printed MNA splint designed for customized curved surfaces, ensuring complete insertion into undulating human skin. In another study aimed at treating skin cancer, was manufactured through SLA 3D printing, followed by the application of the drug (cisplatin) onto the needles using inkjet printing (Uddin et al. 2020). Pere et al. (2018) employed the 3D printing method to fabricate pyramid and cone MNA designs for the delivery of insulin and proved the possibility of using 3D-printed MNA for this application. They fabricated a 25 MN array made of fumaric acid that can withstand the skin-piercing pressure with painless insertion. Wu et al. (2020) fab-

Fig. 2. (A) 3D printed microneedle arrays (MNAs) with different cross-section shapes for detection application, reprinted under a Creative Common License [CC BY] (Razzaghi et al. 2023); (B) (i) a schematic showing the concept of the effect of the printing tilt angle on the needle tip sharpness, (ii) the MNA design for 3D pring with printing tilt angle, (iii) 3D-printed MNA with printed tilt angle, reprinted under a Creative Common License [CC BY] (Razzaghi and Akbari 2023).

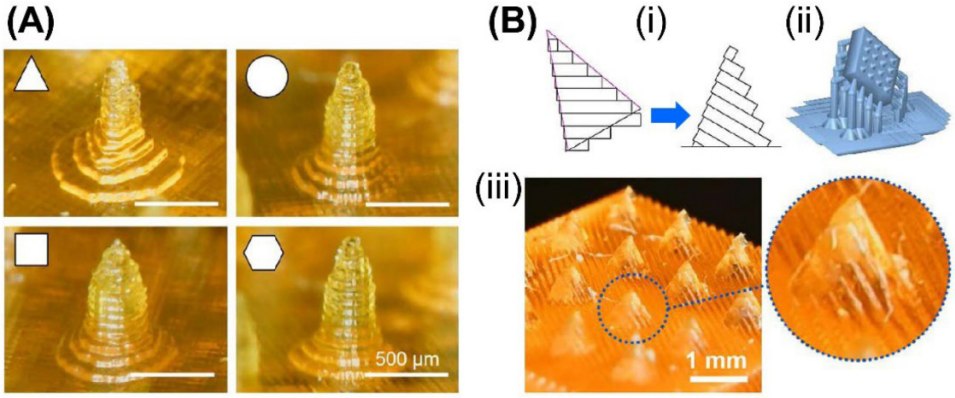
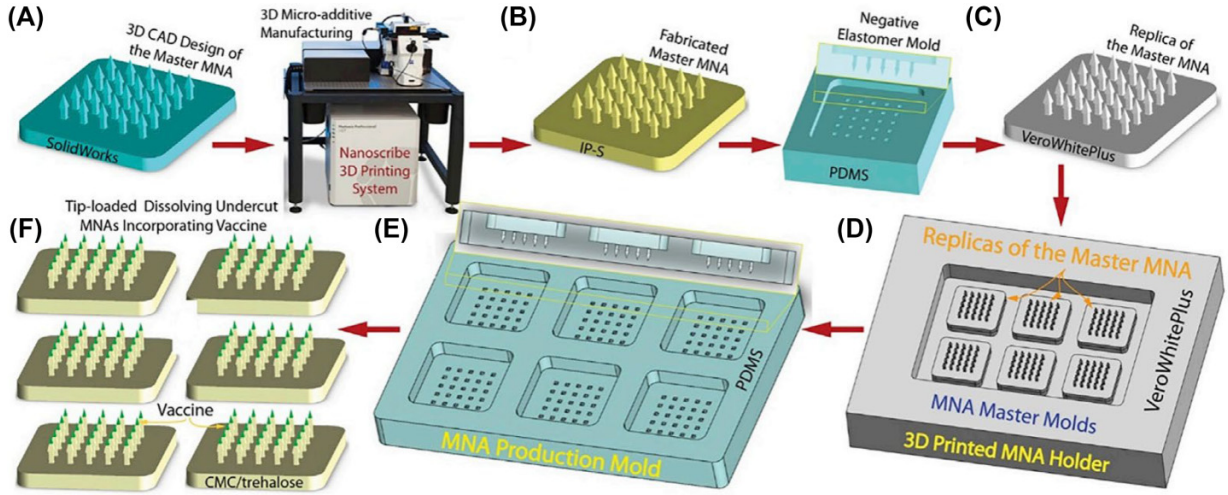


Fig. 3. Microneedle array (MNA) fabrication utilizing combined 3D printing and micromolding, (A) 3D modeling of master MNA using computer-aided design (CAD) software, (B) 3D printing of the designed MNA, (C) replication of the master mold, (D) arrangement of multiple master molds on a holder, (E) manufacture of MNA fabrication mold by polydimethylsiloxane (PDMS), (F) drug loading on the tip of the fabricated MNAs; reprinted with permission from Elsevier (Balmert et al. 2020).



ricated MNAs using an extrusion-type 3D printer for drug delivery application. Their 3D printer had two nozzles; one was utilized for 3D printing the substrate, and the other for printing the drug-contained material.

Our team has focused on employing 3D printing techniques for MNAs across various applications. In one study, we developed 3D-printed MNAs using polyethylene glycol diacrylate (PEGDA), aimed at extracting biomarkers from ISF and detecting them colorimetrically. The results demonstrated the successful identification of biomarkers within the interstitial skin fluid (Razzaghi et al. 2023). The primary challenge in directly 3D printing MNAs lies in the limited sharpness achievable for the needle tips due to the constraints of printing resolution. Our other study aimed to enhance the sharpness of the needles' tips in PEGDA-based 3D printed MNAs, utilizing printing tilt angles and optimizing them. This research revealed a notable improvement in the penetration capability of 3D-printed MNAs into the skin (Razzaghi and Akbari 2023). Figure 2 represents the 3D-printed MNAs discussed in these two studies.

The use of 3D printing extends to the fabrication of MNAs by creating a master mold (Dabbagh et al. 2020). These techniques are suitable for producing a large number of MNA with various materials (Tejavibulya et al. 2019). However, to make any modifications to the geometry of mold-based MNAs, the entire fabrication process of the mold needs to be repeated (Dabbagh et al. 2020). Balmert et al. (2020) employed laser 3D printing and micromolding processes to create undercut MNAs, and their MNA fabrication process is schematically depicted in Fig. 3.

One of the limitations to achieving the desired geometrical requirements of MNAs is the limited resolution of the utilized fabrication route. Apart from numerous studies that have been conducted to improve the resolution of 3D printers

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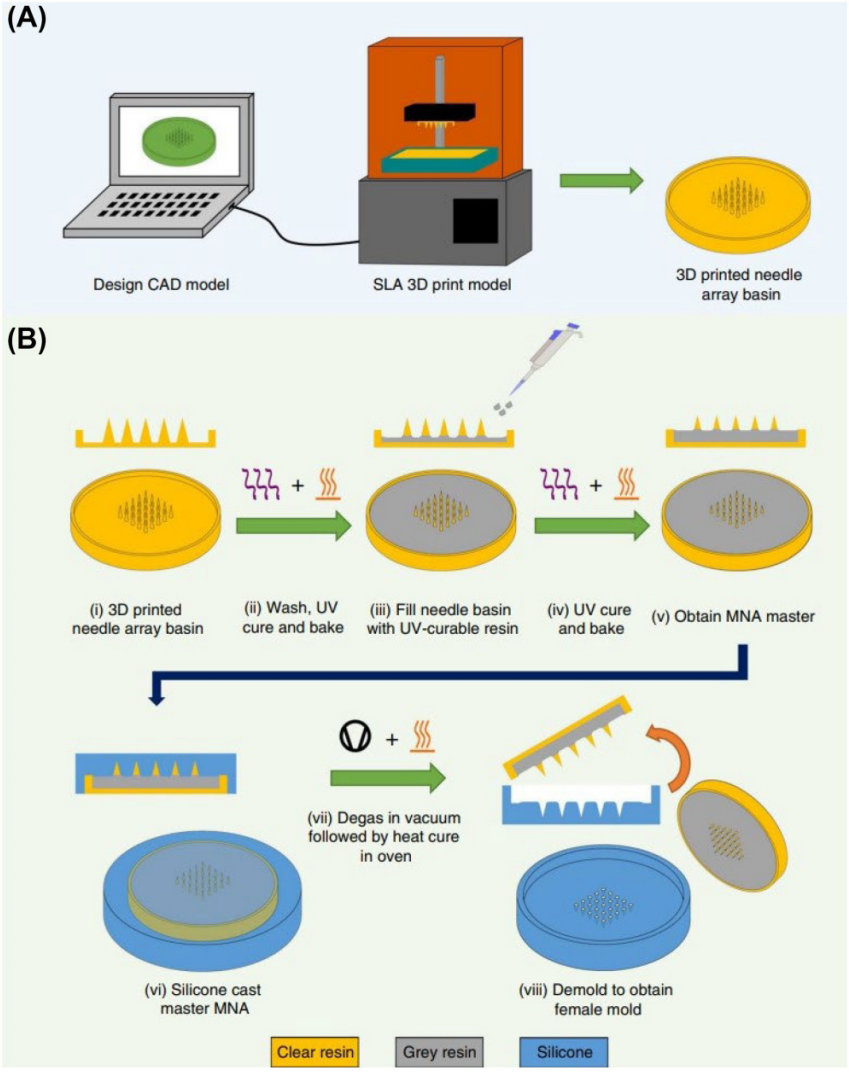
Fig. 4. Illustration of "Print & Fill" fabrication process, (A) microneedle array (MNA) basin design and 3D printing of the design employing a low-price desktop stereolithography (SLA) printer, (B) fabrication method of MNA master mold: (i) taking 3D-printed MNA basin, (ii) washing, ultraviolet (UV) curing and baking of printed MNA basin, (iii) filling of MNA basin with UV-curable resin, (iv) another UV curing and baking, (v) obtaining MNA master, (vi) silicone casting of MNA master, (vii) degassing and heat curing in an oven, (viii) demolding to attain usable MNA mold; reprinted under a Creative Common License [CC BY] license (Krieger et al. 2019).



by manipulating the printer itself (Pere et al. 2018; Serex et al. 2018; Gong et al. 2020), integrating 3D printing with other processes is another way to improve the resolution of the fabricated MNA without modifying the printer (Park et al. 2019). Ochoa et al. (2015) coupled the SLA 3D printing process with an isotropic shrinkage method, which efficiently improved the resolution of 3D printing by at least five-fold. This method consisted of transferring the 3D-printed MNAs to a hydrogel, which shrank by up to 40% within 12 h. Needle patterns were then transferred to a biodegradable poly(vinylpyrrolidone) (PVP) polymer, resulting in MNAs with adequately sharp tips.

In another study, Krieger et al. (2019) presented a customizable, simple method to fabricate MNA utilizing a low-price SLA 3D printer. They introduced a two-step "Print & Fill" mold fabrication process for creating high-aspect-ratio sharp MNAs capable of penetrating the skin using an affordable 3D printer. Figure 4 shows their fabrication process schematically. A study on skin penetration was conducted to demonstrate the functional efficacy of the MNAs prepared using the fabricated mold. Successful insertion of the fabricated MNA showed that the proposed method is feasible for fabricating MNA using low-price 3D printers.

5. Biocompatibility and toxicity of microneedle arrays

Biocompatibility is a fundamental requirement for materials used in MNAs, as it ensures that these materials do not cause harmful biological responses when inserted into the skin. This concept of biocompatibility encompasses a wide

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range of factors, including cytotoxicity, immunogenicity, and the potential to cause allergic reactions or inflammation.

Cytotoxicity refers to the ability of a material to affect human cells. Materials used in MNAs must be non-toxic, meaning they should not harm or kill cells upon contact. Metals like stainless steel and titanium are frequently chosen for their outstanding biocompatibility. These metals have a long history of successful use in medical devices due to their non-toxic nature, making them ideal for applications where prolonged contact with human tissue is required (Salaam et al. 2024). In addition to metals, certain polymers such as PLA, PGA, and polycaprolactone are particularly suitable for microneedle applications. These polymers are both biodegradable and biocompatible, meaning they can safely break down within the body over time without causing harm. This makes them excellent candidates for microneedles that are intended to dissolve after fulfilling their purpose (Koyani 2020).

Concerning immunogenicity, the material should not provoke an immune response that might cause inflammation or rejection (Lock et al. 2019). Materials used in MNAs should be designed in such a way that they do not trigger an unwanted immune response, which could lead to inflammation or even rejection of MNA by the body. For instance, hydrogels made from HA are highly valued for their biocompatibility and have been effectively used in the production of dissolvable MNAs. These hydrogels are particularly advantageous because they minimize the risk of an immune response, thereby reducing the chances of inflammation or other complications (Luo et al. 2023).

Furthermore, the potential for allergic reactions must also be carefully considered when selecting materials for MNAs. Allergic reactions can occur when the body's immune system identifies certain substances as harmful, even if they are not. To minimize the risk of such reactions, materials used in MNAs should be free from known allergens and other potentially harmful substances. Polymers and hydrogels that are derived from natural sources, or those that have been synthesized to closely mimic natural substances, tend to have a lower likelihood of provoking allergic responses. This makes them preferable choices over purely synthetic materials, which may have a higher risk of causing adverse reactions (Aldawood et al. 2021).

The biocompatibility and toxicity of various 3D-printed MNAs have been explored in numerous studies. Zhou et al. (2024) investigated the biocompatibility and cytotoxicity of hydrogel-based MNAs, which were fabricated using a DLP 3D printer. Their findings revealed that these hydrogel MNAs did not exhibit any cytotoxic effects. Similarly, Monou et al. (2024) assessed the biocompatibility of drug-coated MNAs, also 3D printed using a DLP printer. In this study, the MNAs were created with a commercial biocompatible resin known as Dental SG, produced by Formlabs. The MNAs were further coated with a drug using an extrusion 3D printer. The researchers evaluated the toxicity of these MNAs by performing cell studies, as well as histological and immunohistochemistry tests on human skin samples. The results confirmed that the MNAs were safe for transdermal use and did not induce any cytotoxic effects. Additionally, Wang et al. (2024) studied the biocompatibility of silk fibroin MNAs they developed. Their cytotoxicity tests demonstrated that these MNAs were biocompatible and gentle on the skin, making them suitable for long-term health monitoring without causing harmful or irritating effects on the skin.

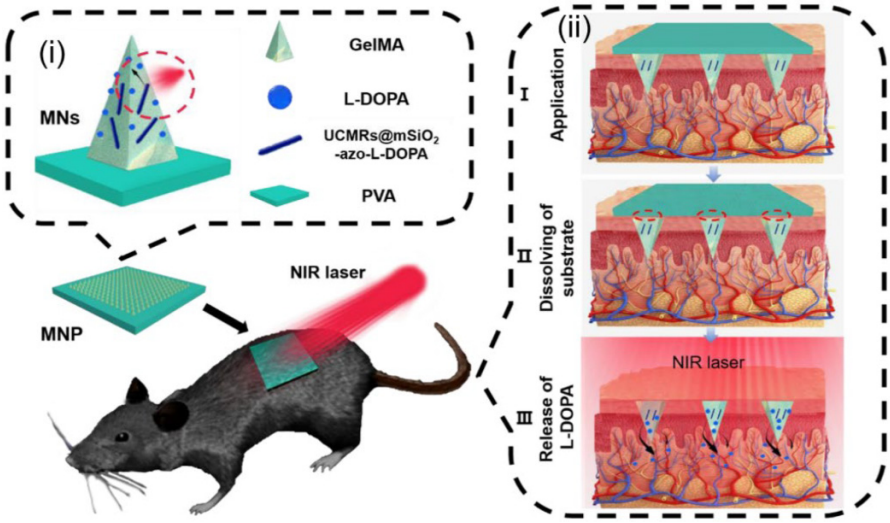
6. Applications of microneedle arrays for drug delivery to the brain

Although the investigation into the use of MNAs for drug delivery to the brain is limited, recent studies have highlighted the potential of MNAs in the treatment of brain diseases. The utilization of MNAs for drug delivery to the brain can take various approaches. Some studies have employed MNAs to transdermally administer drugs into the bloodstream. In such applications, the drugs can efficiently reach the targeted brain site through the circulatory system. For example, Zhou et al. (2022) developed an MNA that could release medications with controlled temporal and spatial precision activated by near-infrared (NIR) light to treat Parkinson's disease. The MNAs matrix was made of gelatin methacryloyl (GelMA), and the drug (L-DOPA) was stored in the mesopore of the upconversion micron-rods (UCMRs), dispersing in the GelMA. The fabricated MNA can penetrate the epidermis in a painless, non-infectious, and non-invasive manner. Under the exposure of NIR light, the drug in the MNAs was released as needed and subsequently absorbed into the bloodstream. The results indicated that the MNA with a controlled drug delivery system might be a candidate strategy for treating Parkinson's disease and can be applied in different related biomedical fields, including epilepsy, Alzheimer's disease, and addiction disorders. Figure 5 shows the process of the research schematically (Zhou et al. 2022).

In a separate investigation, Li et al. (2023) devised an innovative composite delivery system by integrating nanocarrier and microneedle technologies to explore the potential of transdermal drug delivery to the brain. Utilizing PLGA as a carrier, nanoparticle solutions containing paroxetine and rhodamine B were formulated through the emulsification–solvent volatilization method. These nanoparticles were then blended with HA, leading to the development of a PLGA nanoparticulate-based microneedle system via a multi-step decompression-free diffusion process. Their findings demonstrated that these nanoparticles possess the ability to prolong blood circulation and intracerebral retention times, alongside exhibiting certain brain-targeting attributes due to their exceptional physical properties. The integration of MNA technology with nanocarriers introduces innovative concepts for delivery systems aimed at treating central neurological disorders (Li et al. 2023).

In another research, Agrawal et al. (2018) suggested a hypothesis focused on the development of MNAs for targeted drug delivery to the brain. They hypothesized that the drug loaded into the MNAs can simply combine with mononuclear phagocytic cells (macrophages/monocytes; Ma/Mo), which act as nanocarriers to carry the drug to the site of disease. Their hypothesis demonstrated the concept of using MNAs as a distribution platform for delivering the calcium phosphate nanoparticles (CaNPs) drug to macrophages. Once Ma/Mo en-

Fig. 5. Diagram illustrating microneedle arrays (MNAs) designed for controlled release of drugs intended for Parkinson's disease treatment, (i) the components present in MNAs and the backing layer, and (ii) the procedure for applying microneedle patches on the skin of mice, (I) administer the MNAs onto the skin of mice by applying external force, (II) the backing layer dissolves, causing the MNAs that penetrate the skin layer to detach from the backing layer, (III) employ near-infrared (NIR) light to illuminate the area where the MNAs are applied, prompting the MNAs remaining in the epidermis to release the drug; reprinted with permission from Elsevier (Zhou et al. 2022).



gulfs the CaNPs, these cells can carry these particles from the injected area to the inflammatory/diseased site of the brain. Their suggested drug delivery process consists of (1) uptake of MNAs delivered CaNPs by Ma/Mo; (2) migration of drug-loaded Ma/Mo from the skin to the brain parenchyma; (3) CaNPs loaded Ma/Mo infiltration in the brain overcoming BBB; and (4) drug release from the macrophages at the inflammatory/diseased site of the brain. The researchers also used an in situ glioma rat model to test their hypothesis (Agrawal et al. 2018).

Zhang et al. (2022) utilized a calcium channel blocker, cinnarizine, in their research, to create dissolving MNAs for treating microwave-induced brain injury. The cinnarizine MNAs consisted of PVP K90 as the tip and photopolymerized PVP as the base, along with the drug itself. This composition provided high mechanical strength, facilitating easy penetration of the skin on the neck and enabling high drug release in vivo. The application of cinnarizine MNAs significantly enhanced the recovery of spatial memory and spontaneous exploratory behavior in rats following microwave radiation exposure, achieved by inhibiting the expression of calcineurin and calpain-1. The dissolving MNA method shows promise as an effective approach for drug delivery and combating microwave radiation effects (Zhang et al. 2022).

Kearney et al. (2016) presented the preparation and assessment of an MNA containing Alzheimer's disease medication, donepezil hydrochloride. Their MNA was made up of hydrogel MNAs and a drug-containing film. The quantity of plasma concentrations obtained when the MNA was administered to an animal model confirmed the success of this delivery platform for donepezil hydrochloride. The research outcomes showed the possibility and efficacy of drug delivery by MNA for the treatment of Alzheimer's disease.

Also, Yan et al. (2020) evaluated dissolving MNA for delivering the huperzine A medication and investigated its in vitro profiles of drug release and in vivo pharmacokinetics and pharmacodynamics treating Alzheimer's. The outcomes of the skin penetration experiment and intradermal dissolution test revealed that the blank dissolving MNA could successfully pierce the skin with an acceptable depth and quickly dissolve in 5 min. Also, the results of the in vitro transdermal release experiment showed that more than 80% of the drug had been accumulatively released from dissolving MNA through the skin within 3 days, signifying a sustained release profile. The research results revealed that the transdermal drug delivery strategy with dissolving MNA is capable of remarkably improving the bioavailability of huperzine A compared to its oral administration and accomplishing a desirable sustained release in a painless and minimally invasive manner (Yan et al. 2020).

Some other studies have utilized MNAs as an intranasal drug delivery device for delivering drugs to the brain. Based on this approach, Permana et al. (2023) devised an innovative method combining PLGA-based nanoparticles (PLGA-NPs) containing rivastigmine with HA-based two-layered dissolving MNAs to efficiently deliver rivastigmine via the trigeminal pathway from the nasal cavity to the brain through the mystacial pad region. Various evaluations were conducted to optimize the formulations, resulting in nanoparticles with a particle size below 200 nm and a sustained release of rivastigmine from the PLGA-NPs reaching up to 95.42 $\pm$ 8.76% after 48 h. Upon integration of PLGA-NPs into HA-based MNAs, the formulations exhibited suitable mechanical and insertion properties, demonstrating the viability of the system. Ex vivo studies revealed that MNAs displayed superior dermatokinetic profiles compared to needle-free patch formu-

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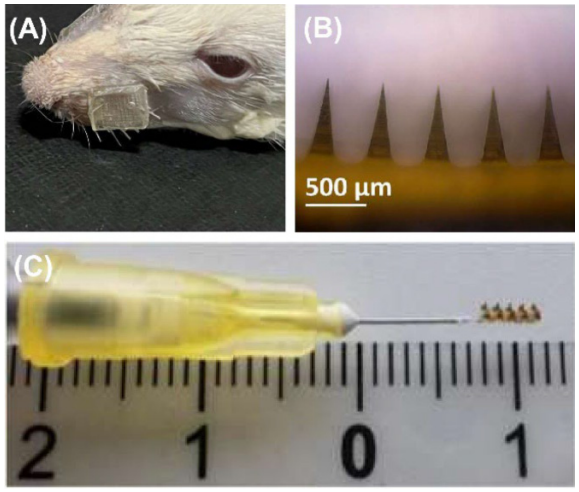
Fig. 6. (A) Application of microneedle arrays (MNAs) into mystacial pad region of the rats; (B) light microscope image of MNAs prepared from hyaluronic acid (HA) and poly(vinylpyrrolidone) (PVP); reprinted with permission from Elsevier (Permana et al. 2023); (C) appearance of a flexible MNA fabricated into toothbrush-shaped patch adhesive to a disposable sterile syringe needle for intranasal drug delivery to the brain; reprinted with permission from Elsevier (Ruan et al. 2024).



lations. Furthermore, the formulations demonstrated cytocompatibility with neuro-2a and hCMEC/D3 cell lines. Notably, in vivo studies demonstrated significantly enhanced brain targeting efficiency, with drug targeting efficiency values exceeding 60-fold and direct transport percentages exceeding 90% compared to conventional oral administration, injection, and polyvinyl pyrrolidone-based MNAs, without adverse effects on the brain as evaluated through histopathology. These findings underscore the advantages of delivering rivastigmine through the trigeminal pathway to the brain using the combination of PLGA-NPs and two-layered MNAs, offering a promising novel approach for Alzheimer's disease treatment with numerous benefits over conventional oral rivastigmine preparations. Figure 6A shows the application of the developed MNAs into mystacial pad region of the rats and Fig. 6B shows the image of MNA (Permana et al. 2023).

In another study, Ruan et al. (2024) devised dissolving microneedles paired with nanocarriers to enhance transnasal drug delivery to the brain. They created a toothbrush-like MNA comprising HA-formed MNs and a tannic acid-crosslinked gelatin base. This design facilitated transnasal administration, as the microneedles dissolved rapidly in the nasal mucosa, leaving only the base, thereby releasing the loaded cyclodextrin-based metal-organic frameworks (CD-MOFs) without affecting nasal cilia or microbial communities. The CD-MOFs function as nano-carriers for efficiently loading huperzine A. These carriers are composed of potassium, strengthened by stigmasterol, and modified with lactoferrin, thereby ensuring improved physical stability and exceptional compatibility with biological systems, facilitating effective delivery of drugs targeted to the brain. The applied system for drug delivery notably mitigated neurocyte damage induced by H_2O_2 and scopolamine. Moreover, it significantly improved the efficacy of huperzine A in ameliorating memory deficits induced by scopolamine and D-galactose and $AlCl_3$ in rats. This advancement was demonstrated through the inhibition of acetylcholinesterase activity, reduction of oxidative stress in the brain, improvement in learning function, and activation of the extracellular regulated protein kinases-cyclic adenosine monophosphat responsive element binding protein-brain-derived neurotrophic factor pathway. Additionally, an increase in the expression of postsynaptic density protein PSD-95, which interacts with crucial therapeutic targets Tau and β-amyloid in Alzheimer's disease, was observed. This holistic treatment strategy not only surmounted obstacles to effective drug delivery to the brain but also underscored the potential therapeutic efficacy of huperzine A in Alzheimer's disease. Figure 6C shows the appearance of the developed MNA fabricated into toothbrush-shaped patch adhesive to a disposable sterile syringe needle for intranasal drug delivery to the brain (Ruan et al. 2024).

Some other studies have tried to use MNAs locally on the brain tissue for delivering the drug. The unique design of MNAs, with multiple protrusions, holds promise for achieving uniform drug delivery with enhanced penetration. By piercing the brain tissue, conforming to the brain parenchyma, and remaining in place until the entire drug payload is released, microneedles offer remarkable improvements compared to existing technologies like the Gliadel® wafer. The development of materials capable of traversing the BBB to treat brain tumors has been a major focus. However, the BBB also poses a challenge in the penetration of chemotherapeutic drugs into brain tissue for the treatment of brain diseases (Banks 2016; Jiang et al. 2023). To address these challenges, Lee et al. (2015) designed thin microneedles based on silicon, utilizing a glass cover on silicon technology to embed microchannels that enable the delivery of trypan blue dye deep into the brain of a mouse model. These microneedles had dimensions of 5.3 mm in length, 40 µm in thickness, and 70 µm in width. The study demonstrated precise control over decreasing flow rates, indicating the potential for delivering small amounts of drugs. Experiments conducted in 0.9% *w*/*v* agarose gel and mouse brain confirmed the ability of these microneedles to diffuse and deliver trypan blue dye to the desired brain region with minimal damage to the brain tissue. Consequently, these fabricated microneedles hold promise for the delivery of drugs and even viruses to specific areas of the brain.

Furthermore, in an effort to tackle the challenge of delivering anti-tumor drugs to brain tumors, Lee et al. (2021) developed a method utilizing two types of MNAs for local delivery: therapeutic bioabsorbable MNAs and stimulating light-guiding/spreading MNAs. Their outcomes showed that bioabsorbable MNAs made with HA through a two-step molding process, can bypass the BBB and deliver therapeutic NPs directly to brain tumors. On the other hand, light-guiding/spreading MNAs made with a photocurable transparent polymer, generate high-energy photons that disperse and diffuse within the surrounding tumor tissues. To enhance the spreading of photons, alumina (Al_2O_3) microparticles were

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embedded into the light-guiding/spreading MNAs. Once implanted, light-guiding/spreading MNAs activated therapeutic NPs through high-energy photons following the dissolution of bioabsorbable MNAs.

In another research, Wang et al. (2020) presented a heterogeneous silk MNA for the postoperative and minimally invasive treatment of brain gliomas. They demonstrated the capability to incorporate numerous drugs into the silk MNA either separately or at the same time, ensuring precise control over their release patterns, including variations in drug types and customizable dosages as needed. Their proposed MNA can be inserted directly into the tumor cavity and degrade completely after use in a programmable manner. The customizable mechanical characteristics of the fabricated MNA allow it to enter brain tissue and conformally bind to the curved brain surface. They showed that the tumor microenvironment could be effectively modulated by the controlled release of various medications while avoiding the hurdles of the BBB. This silk MNA opens up new possibilities for the precise delivery of various medications for intracranial brain tumor treatment in situ (Wang et al. 2020). In another study, Wang et al. (2021) developed a silk MNA with various drug release kinetics for in situ glioma treatment. They implanted the fabricated MNA in a mouse model and showed that the multidrug MNA could efficiently improve treatment even at lower doses. The outcomes of the research showed that the presented MNA had much promise as a novel class of therapeutic treatment of glioma. The method can bypass the BBB, allowing the loaded medications to be delivered directly into the tumor cavity with variable release kinetics. In a tumor mouse model, it inhibited glioma cell multiplication, increased survival time, and improved cure rate. In this study, three individual medications, including temozolomide, bevacizumab, and thrombin, were combined with a silk protein solution to create functionalized silk ink, which was then precisely injected into different mold cavities to create the silk MNA (Wang et al. 2021).

In a separate study, Muresan et al. (2023) developed polymeric MNAs designed to be implanted within a resection cavity after the surgical removal of tumors like isocitrate dehydrogenase wild-type glioblastoma. These MNAs were loaded with polymer-coated NPs containing either cannabidiol or olaparib and tested on an in vitro brain simulant and ex vivo rat brain tissue to evaluate drug release and penetration distance. MNAs loaded with methylene blue dye were inserted into a 0.6% agarose cavity to mimic brain tissue. The outcomes revealed that the MNAs created clear channels, allowing the dye to spread laterally throughout the agarose. When loaded with cannabidiol-NPs, the agarose exhibited a cannabidiol concentration of 12.5 μg/g at a distance of 0.5 cm from the microneedle insertion site. Moreover, high-performance liquid chromatography analysis of ex vivo brain tissue following cannabidiol NP/MNA insertion demonstrated successful delivery of 59.6 μg/g into the brain tissue. Similarly, olaparib -NP loaded MNA facilitated the delivery of 5.2 μg/g olaparib into agarose gel at a distance of 0.5 cm from the insertion site. Orbitrap secondary ion mass spectrometry analysis confirmed the presence of olaparib and the MNA up to 6 mm away from the insertion site after application to a rat brain hemisphere. These data shed light on the potential of MNAs for localized brain drug delivery, offering promise for future research. The Figs. 7A and 7B show the placement of these MNAs onto rat brain hemispheres (Muresan et al. 2023).

Also, Sarker et al. (2023) introduced a novel hybrid additive manufacturing method that merges DLP 3D printing with ex situ direct laser writing to create innovative types of MNAs for fluidic microinjections. They fabricated MNAs with inner diameters of 30 μm, outer diameters of 50 μm, heights of 550 μm, and needle-to-needle spacing of 100 μm, and DLP-printed capillaries demonstrated preserved fluidic integrity at the MNA-capillary interface under microfluidic cyclic burst-pressure testing, even at input pressures exceeding 250 kPa ($n = 100$ cycles). Ex vivo tests conducted on excised mouse brains revealed that these MNAs not only endured penetration into and retraction from brain tissue but also facilitated effective and uniform microinjection of surrogate fluids and nanoparticle suspensions directly into the brains. Taken together, these outcomes indicated that the proposed approach for manufacturing high-aspect-ratio, high-density, hollow MNAs shows great promise for various biomedical microinjection applications. Figure 7C shows the MNA-capillary assembly connected to a custom-built nanoinjector alongside an excised mouse brain on ice and Fig. 7D shows the scanning electron microscopy (SEM) image of the DLP-printed MNA designed for drug delivery to the brain (Sarker et al. 2023).

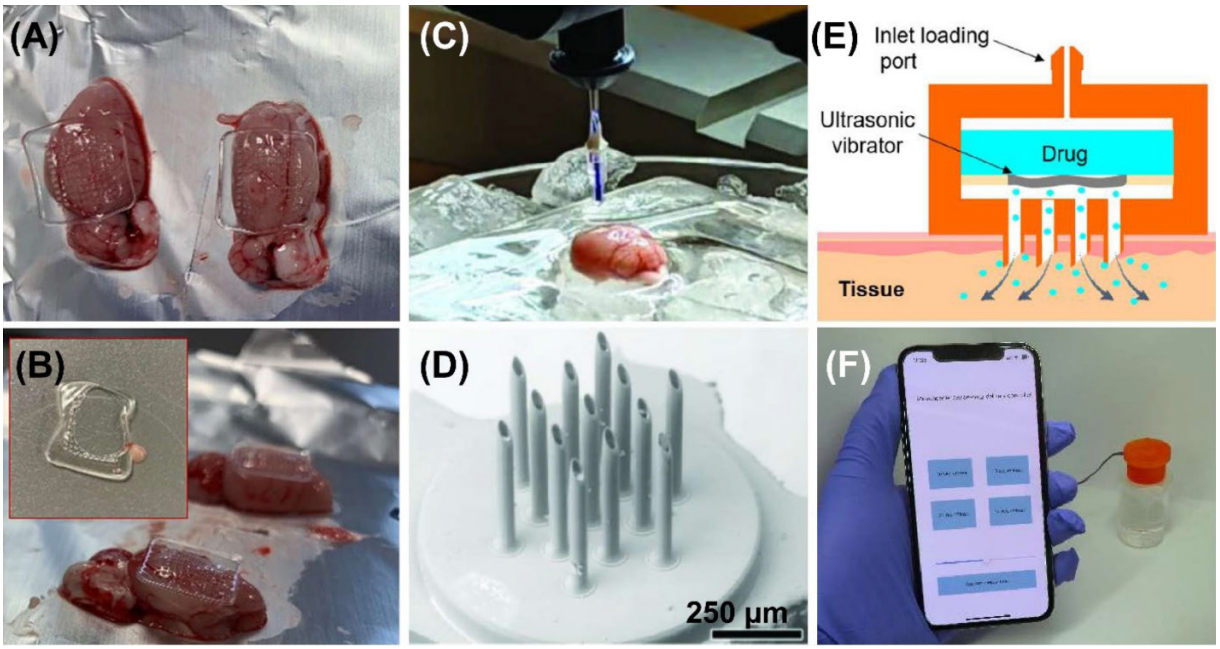
In recent research, our team developed a novel pumpless drug delivery system using hollow MNA that could be used for brain drug administration. This study introduces a new remote healthcare device featuring a type of MNA for both drug delivery and biomarker detection. The incorporation of an ultrasonic atomizer simplifies the MNA, enabling fast, pumpless, and point-of-care drug delivery, which improves portability and reduces complexity. A smartphone application is used to interface with the sensing and drug delivery components. Figure 7E presents a schematic illustration of the mechanism underlying the developed drug delivery system, while Fig. 7F displays the interface of the smartphone application used for remotely controlling the system (Razzaghi et al. 2024).

Table 1 provides a summary of research that has investigated drug delivery to the brain using MNAs.

7. Summary, challenges, and future aspects

Oral and conventional syringe administration has several limitations and disadvantages. Drug delivery to the brain possesses a number of challenges, including the BBB's restrictive nature, limiting the entry of therapeutic agents. The complex and delicate nature of brain tissue adds complexity, requiring precise and targeted delivery methods. Additionally, the potential for local toxicity and inflammation necessitates careful consideration in developing effective strategies. Overcoming these challenges is essential for enhancing the efficacy of brain drug delivery, improving patient outcomes, and advancing neurotherapeutics. Fabrication and development

Fig. 7. (A) Placement of microneedle arrays (MNAs) onto rat brain hemispheres from an overhead perspective; (B) placement of MNAs from a lateral viewpoint, with an inset demonstrating the inability to remove the MNA due to its adherence to the tissue and the dissolution of the MNA, reproduced with permission from Elsevier (Muresan et al. 2023); (C) experimental arrangement illustrating the MNA-capillary assembly connected to a custom-built nanoinjector alongside an excised mouse brain on ice; (D) SEM image displaying representative fabrication outcomes, featuring a digital light processing (DLP)-printed MNA designed for drug delivery to the brain, reprinted with permission from Wiley (Sarker et al. 2023); (E and F) remote-controlled MNA device that could be used for drug delivery to the brain, reprinted with permission from Wiley (Razzaghi et al. 2024).



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of MNAs could overcome the drawbacks of traditional drug delivery methods. MNAs have many advantages such as increased patient comfort, lower risk of microbial infiltration into delivery sites, the possibility of delivering multiple drugs simultaneously and delivering in a controlled release manner. MNAs have been used to deliver a wide range of different medications, including brain-targeted drugs. Drug delivery to the brain, using MNAs, include localized delivery of the drugs that need surgery, intranasal delivery and targeted drug delivery methods based on delivering the medication through the body's circulation system. There is limited evidence for the localized drug delivery using MNAs without passing the body's circulation system, and the claim has been only on the comparatively higher accumulation of the drug in the tissue in the proximity of the applied MNA on the skin as the drug first enters the local tissue and then is distributed around the body through the body's circulation system. Hence, further studies are required to investigate the possibility of using MNAs in a non-invasive route for the delivery of the drug to the brain to circumvent the BBB and avoid possible side effects of passing drugs through the circulation system.

Conventional techniques for manufacturing MNAs are intricate and costly. The substantial expenses associated with equipment procurement and maintenance pose a considerable hurdle for those entering the realm of microneedle research, thus constraining mass production capacities to select companies. With advancements in 3D printing technology, microneedle manufacturing has become feasible using entry-level 3D printers, which are more affordable and easier to maintain. Computer-aided design (CAD) software allows for the creation of innovative microneedle shapes, and 3D printing facilitates rapid prototyping and modification, significantly reducing product development time. Nonetheless, limitations exist, including material constraints and the relatively low resolution of entry-level 3D printers. While high-resolution 3D printers are available, they come at a higher cost. Despite these challenges, ongoing research in 3D printing aims to overcome these limitations. It is anticipated that advancements in 3D printing technology will enable the production of personalized microneedle patches tailored to individual needs (Jung and Jin 2021).

However, there are some challenges for the mass production of MNAs. Scaling up the production of MNSs presents several challenges due to the lack of standardized manufacturing methods and the complexities associated with the production processes. Many MNA developers still rely on manual, lab-scale fabrication techniques that are unsuitable for mass production. The variation in MNA designs, formulations, and use cases necessitates the development of custom equipment and novel processes for production. For example, dissolvable MNAs require extended drying times, which complicates the scaling process. Additionally, the scarcity of contract manufacturing organizations with MNA manufacturing capabilities further exacerbates the challenge, as these organizations are reluctant to invest in specialized equipment with-

Table 1. Summary of research on drug delivery to the brain using microneedle arrays (MNAs).

Application	MNA type/method	Drug/compound delivered	Key findings	Study
Parkinson's disease treatment	GelMA MNAs with UCMRs	L-DOPA	Controlled drug release activated by NIR light for Parkinson's disease. Can be applied to other neurological conditions.	Zhou et al. (2022)
Neurological disorders	PLGA nanoparticulate-based MNAs	Paroxetine, rhodamine B	Prolonged blood circulation and brain targeting. Integrates MNA with nanocarriers for treating neurological disorders.	Li et al. (2023)
Drug delivery to brain	MNAs with calcium phosphate nanoparticles (CaNPs)	–	MNAs used to deliver CaNPs to macrophages, which transport drugs to brain sites.	Agrawal et al. (2018)
Brain injury recovery	Dissolving MNAs	Cinnarizine	Enhanced recovery from brain injury by inhibiting specific proteins. Effective and minimally invasive drug delivery.	Zhang et al. (2022)
Alzheimer's disease treatment	Hydrogel MNAs with drug-containing film	Donepezil hydrochloride	Effective transdermal delivery for Alzheimer's disease. Confirmed by plasma concentration studies.	Kearney et al. (2016)
Cognitive enhancement	Dissolving MNAs	Huperzine A	Improved bioavailability and sustained release compared to oral administration.	Yan et al. (2020)
Brain targeting and Alzheimer's disease	HA-based MNAs with PLGA-NPs	Rivastigmine	Enhanced brain targeting through the trigeminal pathway. Superior to traditional methods in efficiency and safety.	Permana et al. (2023)
Memory improvement	HA-based MNAs with CD-MOFs	Huperzine A	Effective transnasal delivery, improved memory and reduced neurocyte damage.	Ruan et al. (2024)
Targeted brain region treatment	Silicon-based MNAs	Trypan blue dye	Precise control of drug delivery to specific brain regions with minimal damage.	Lee et al. (2015)
Brain tumor treatment	Bioabsorbable and light-guiding/spreading MNAs	Therapeutic NPs	Delivered NPs to brain tumors, light-guiding MNAs activated therapeutic NPs.	Lee et al. (2021)
Glioma treatment	Silk MNAs	Various drugs	Customizable drug release for glioma treatment, programmable degradation, effective tumor treatment.	Wang et al. (2020)
Glioma treatment	Silk MNAs	Temozolomide, bevacizumab, thrombin	Improved glioma treatment, effective at lower doses, bypassed the BBB.	Wang et al. (2021)
Localized brain treatment	Polymeric MNAs	Cannabidiol, olaparib	Successful localized delivery to brain tissue, effective penetration and drug release.	Muresan et al. (2023)
Microinjection in brain tissue	DLP-printed MNAs with fluidic microinjection	Surrogate fluids, NPs	High-density MNAs for microinjection, durable and effective in brain tissue.	Sarker et al. (2023)

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out established precedents, leading to high investment risks (Creelman et al. 2022).

Navigating regulatory concerns is equally challenging for the MNA industry, particularly due to the lack of established guidelines and precedents for this technology. Regulatory bodies have yet to clearly define the sterility requirements for MNAs, which fall between traditional transdermal patches and injectable technologies. The uncertainty surrounding these requirements poses significant risks for developers, who must choose between costly aseptic manufacturing or a potentially non-compliant low-bioburden process. Furthermore, quality control methods are still under development, with a need for technological advancements in non-destructive in-line quality control to ensure consistent product quality. The absence of standardized regulatory pathways hinders the industry's ability to achieve widespread approval and commercial production of MNAs (Creelman et al. 2022).

At present, the licensing process for microneedle products is conducted on a per-application basis rather than for specific microneedle systems (product-specific approval). Consequently, this fragmented approach to licensing leads to delays, hindering the commercialization of microneedles. To tackle this issue, a comprehensive regulatory framework for microneedle-based licensing is necessary, encompassing aspects such as shape, formulation, sterilization, and packaging. By integrating current Good Manufacturing Practice standards and quality control measures, a licensing approach for microneedles based on quality by design should be implemented. This strategic shift aims to facilitate the commercialization of microneedle products as pharmaceuticals (Jung and Jin 2021).

Due to their diminutive size, MNAs have a restricted capacity for drug delivery, posing challenges when large doses or sustained release are necessary. One approach to surmounting this constraint is by employing multiple patches simultaneously or periodically replacing the microneedle patch. Nevertheless, to broaden the utility of MNAs, further investigation is required to enhance the drug dosage that can be accommodated within microneedles (Jung and Jin 2021).

While MNAs offer promising solutions for drug delivery, significant challenges remain. Further research is essential to address issues such as scaling up production, navigating regulatory frameworks, and improving drug dosage capacity. Continued advancements are needed to fully harness the potential of MNAs in various medical applications.

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Author contributions

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